# CHRONIC COMPLICATIONS IN DIABETES MELLITUS

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# DM COMPLICATIONS

- PREVENTION
- PREVENTION
- PREVENTION
- PREVENTION
- PREVENTION
- PREVENTION
- MANAGEMENT

# DM COMPLICATIONS - EPIDEMIOLOGY

- MAJOR DETERMINING FACTORS
  - Duration
  - Glycemic Control
  - Type 1 vs. Type 2

# DM COMPLICATIONS - GLYCEMIC CONTROL IN TYPE 1

- DIABETES CONTROL AND COMPLICATIONS TRIAL (DCCT)
  - 1441 pts. with type 1 DM
  - 726 within 5 years of onset = 0 comp's
  - Comparison of intensive therapy vs.... conventional therapy
  - Mean follow-up 6.5 years (4-9) with 98% data collection

# DM COMPLICATIONS - GLYCEMIC CONTROL IN TYPE 1

- DIABETES CONTROL AND COMPLICATIONS TRIAL (DCCT)
- INTENSIVE THERAPY MEANS
  - Subcutaneous Continuous Insulin Injection (pump) OR
  - Multiple daily injections AND
  - Monthly clinic visits

# DM COMPLICATIONS - GLYCEMIC CONTROL IN TYPE 1

- DCCT RESULTS:
- INTENSIVE GROUP:
  - HgA1c avg..... 7.2%
  - FS avg..... 155 mg/dl
- CONVENTIONAL GROUP:
  - HgA1c avg..... 9.1%
  - FS avg..... 231 mg/dl

# DM COMPLICATIONS - GLYCEMIC CONTROL IN TYPE 1

- **DCCT RESULTS:**
- **In Intensive Group:**
- **Retinopathy progressed by 3 steps in 70.3% fewer patients.**
- **Initial appearance of retinopathy was reduced by 27%.**
- **Need for laser photocoagulation reduced by 56%.**

# DM COMPLICATIONS - GLYCEMIC CONTROL IN TYPE 1

- **DCCT RESULTS:**
- **In Intensive Group:**
- **Nephropathy (albuminuria > 300 mg/d) reduced by 54%.**
- **Neuropathy (Nerve conduction abnormalities + clinical sx.) reduced by 64%.**

# DM COMPLICATIONS - GLYCEMIC CONTROL IN TYPE 1

- **DCCT RESULTS:**
- **In Intensive Group:**
- **Macrovascular events (cardiac & peripheral) reduced; though not to statistically significant level.**
- **Significant LDL elevation (>160 mg/dl) reduced by 35%.**

# DM COMPLICATIONS - GLYCEMIC CONTROL IN TYPE 2

- DCCT looked at Type 1 only!
- Can we apply findings to type 2?
- Studies:
  - Small Japanese study with 110 patients shows results similar to DCCT.
  - UKPDS

# UKPDS

- Microvascular Disease
  - Delayed retinopathy
  - Delayed nephropathy
- Macrovascular Disease
  - No effect on:
    - Cardiovascular disease
    - Diabetes-related deaths
    - All-cause mortality
    - Difference in HGB-A1C(0.9%)

# UKPDS

- Macrovascular Disease
  - Metformin +Sulfonylurea detrimental
- Metformin monotherapy showed significant benefit on:
  - Cardiovascular disease
  - Diabetes-related death
  - All cause mortality

# DM COMPLICATIONS - MECHANISMS

- Many different tissues involved - nerves, skin, retina, kidney, heart, brain.
- Common to all of these are:

**BLOOD VESSELS**

# DM COMPLICATIONS - MECHANISMS

- Microvascular Damage Affects:
  - Retinas
  - Glomeruli
  - Nerves

# DM COMPLICATIONS - MECHANISMS

- Microvascular Damage Causes:
  - Blindness
  - End-Stage Renal Disease
  - Neuropathy >>> Amputations

# DM COMPLICATIONS - MECHANISMS

- Macrovascular Damage Affects Large (Named) Arteries:
  - Coronary Arteries
  - Carotid/Cerebral Arteries
  - Lower Extremity Arteries

# DM COMPLICATIONS - MECHANISMS

- Macrovascular Damage Causes:
  - Angina, Myocardial Infarction, Sudden Death
  - Strokes
  - Poor Healing from Wounds or Infections >>> Amputations

# DM COMPLICATIONS - MECHANISMS

- So HOW does diabetes damage blood vessels?
- Best understood mechanism is by non-enzymatic glucosylation (glycation) of proteins and other macromolecules.
- Other mechanisms postulated include changes in NADP+ and NADH levels associated with alternative glucose metabolic fates when usual pathways are saturated.

# DM COMPLICATIONS - MECHANISMS

- Chronic hyperglycemia causes increased glycation of proteins, resulting in Advanced Glycation Endproducts (AGEs)
- These can cause damage through loss of function, turning on/off signal pathways within cells, or alteration in gene expression.

# DM COMPLICATIONS - MECHANISMS

- One of the proteins which is glycated is Hemoglobin. Because it is found in the blood, it is convenient to measure as HgA1c.
- Because RBCs (and thus Hg) survive in the blood for 90-120 days, the HgA1c provides a means to assess glycemic control over this period.

# DM COMPLICATIONS - MECHANISMS

- The Role of Insulin
  - High insulin levels as seen in insulin resistance MAY be contributory to the development of:
    - Hypertension
    - Atherosclerosis

# DM COMPLICATIONS - MECHANISMS

- The Role of Insulin
  - Hyperglycemia causes complications
  - Insulin causes complications
- Type 1
  - Usually not hyperinsulinemic; therefore concentrate on controlling hyperglycemia.
- Type 2 (Actively under investigation)
  - Unclear whether increasing insulin to achieve normal sugars overall benefit!!!

# DM COMPLICATIONS - EYE DISEASE

- 8,000 new cases of blindness due to DM per year in the US.
- 12% Cases of new blindness due to DM.
- Leading Cause of new Blindness in working-aged Americans.

# DM COMPLICATIONS - EYE DISEASE

- Early Changes (normal exam)
  - Loss of Autoregulation of blood flow.
  - Decreased blood flow.
  - Loss of pericytes (supporting cells).

# DM COMPLICATIONS - EYE DISEASE

- Nonproliferative Changes:
  - Dot & blot hemorrhages
  - Cotton-wool spots
  - Venous Loops
  - Venous Tortuosity
- 100% incidence at 15 years
  - Increased retinal blood flow.
  - Capillary Dropout

# DM COMPLICATIONS - EYE DISEASE

- **Proliferative Changes**
  - **Neovascularization - most prominent at border between perfused and nonperfused retina.**
  - **Vitreous hemorrhage due to fragility of new vessels.**
  - **Contraction of co-existing glial tissue may lead to retinal detachment.**

# DM COMPLICATIONS - EYE DISEASE

- **Quiescent Stage**
  - **End of Proliferative changes; vision usually stable at whatever level of loss was sustained during proliferative phase.**
  - **Laser photocoagulation seems to accelerate transition from proliferative phase to quiescent phase. Intent is to arrive at quiescent phase with minimal loss of vision.**

# DM COMPLICATIONS - EYE DISEASE

- **Macular Edema**
  - In DM, retinal vessels are more permeable.
  - Fluid leakage from vessels to retina can cause localized edema.
  - If present in the macula, can cause reduction in VA (20/20 > 20/50).
  - Affects 300,000 pts/year.
  - Risk can be decreased with laser rx.

# DM COMPLICATIONS - EYE DISEASE

- PREVENTION STRATEGIES:
  - Glycemic Control
  - Regular Eye Exams
  - Photocoagulation for Macular Edema or Neovascularization

# DM COMPLICATIONS - KIDNEY DISEASE

- Leading Cause of End Stage Renal Disease (ESRD) in developed nations.
- 27.2% Dialysis Patients have DM.
- 36.4% NEW ESRD cases are related to DM.
- Familial clustering occurs.

# DM COMPLICATIONS - KIDNEY DISEASE

- Type 1 vs. Type 2
  - Previous studies suggested higher rate of ESRD in Type 1 pts.
  - More recent studies suggest ESRD rate in Type 2 pts. approaching that in Type 1 pts.

# DM COMPLICATIONS - KIDNEY DISEASE

- To B (for biopsy) or not to B
- Not needed in typical cases (~ 80%)
  - DM > 10 years
  - Other “opathies” present
  - Gradual progression
- Helpful in atypical cases
  - Within 10 yrs. onset of DM
  - Other indicators of inflammatory process
  - Rapid Progression

# DM COMPLICATIONS - KIDNEY DISEASE

- Progression in Type 1 DM
- Glomerular Hyperfiltration
  - Renomegaly
  - GFR up to 140% of normal
  - Intermittent microalbuminuria (with hyperglycemia)

# DM COMPLICATIONS - KIDNEY DISEASE

- Progression in Type 1 DM
- Early Glomerular Lesions
  - Basement Membrane Thickening
  - Exercise-Induced Microalbuminuria
  - Begins ~ 18-24 months after onset DM
  - Lasts 4-15 years

# DM COMPLICATIONS - KIDNEY DISEASE

- Progression in Type 1 DM
- Microalbuminuric Stage
  - 30 - 300 mg Albumin/Day
  - GFR usually maintained
  - Associated with other organ damage

# DM COMPLICATIONS - KIDNEY DISEASE

- Progression in Type 1 DM
- Clinical nephropathy
  - > 300-500 mg/day
  - Falling GFR (~1 ml/min/month)
  - Nephrotic Syndrome may occur
    - * >3500 mg/day
    - * Hypoalbuminemia
    - * Edema
    - * Hyperlipidemia

# DM COMPLICATIONS - KIDNEY DISEASE

- Progression in Type 1 DM
- E nd S tage R enal D isease
  - Type 1 - 30-40% pts. after 20-30 years.
  - Onset within 2-3 years after nephrotic syndrome.

# DM COMPLICATIONS - KIDNEY DISEASE

- **Progression in Type 2 DM**
- **Not as well-defined as for Type 1 due to unknown onset in many individuals.**
- **20-37% have microalbuminuria AT TIME OF DIAGNOSIS.**
- **Subgroups at higher risk include African-Americans, Hispanics, and Pima Indians.**

# DM COMPLICATIONS - KIDNEY DISEASE

- **Prevention Strategies:**
  - Normalize Blood Pressure
    - Goal 120-130/80-85
    - ACE inhibitors particularly beneficial
  - Dietary Protein Restriction
    - 0.6-0.8 gm/kg/day in established macroalbuminuria or falling GFR
  - Glycemic Control
  - Regular Monitoring for Nephropathy
  - Avoid Nephrotoxins (NSAIDs, some abx)

# DM COMPLICATIONS - NEUROPATHIES

- CNS Complications:
- Stroke
  - Increased Risk (independent of HTN, etc.)
  - Worsened neurologic injuries/deficits
- Diabetic Encephalopathy
  - Subtle cognitive defects
  - Possible increased risk from repeated episodes of severe hypoglycemia
- CNS infections - Mucormycosis

# DM COMPLICATIONS - NEUROPATHIES

- Peripheral Neuropathies:
  - Sensory Loss
    - Pain Reception
      - Pain, Paresthesias
      - Loss of Sensation, Occult Injuries/Ulcers
    - Position/Vibratory Sense
      - Ataxia
      - Increased Falls Risk

# DM COMPLICATIONS - NEUROPATHIES

- Peripheral Neuropathies:
  - Motor Neurons
    - Proximal Motor Neuropathy
      - Pain/Anesthesia anterior thigh
      - Difficulty rising from squat/ climbing stairs
      - Knee Buckling

# DM COMPLICATIONS - NEUROPATHIES

- Autonomic Neuropathies:
  - Cardiovascular
    - Postural Hypotension
    - Resting Tachycardia
    - Painless MI
  - Respiratory
    - Sleep Apnea

# DM COMPLICATIONS - NEUROPATHIES

- Autonomic Neuropathies:
  - GastroIntestinal
    - Esophageal Dysmotility
    - Gastroparesis
    - Pylorospasm
    - Intestinal - Diarrhea, Spasm
    - Gall Bladder Contractility
    - Anorectal Dysfunction - Incontinence

# DM COMPLICATIONS - NEUROPATHIES

- Autonomic Neuropathies:
  - GenitoUrinary
    - Bladder Dysfunction
    - Male Impotence
    - Ejaculatory Disorders
    - Reduced Vaginal Lubrication, Dyspareunia

# DM COMPLICATIONS - NEUROPATHIES

- Prevention Strategies
  - Glycemic Control
  - Smoking Cessation
  - Regular Sensory Exams
  - Personal Protection
  - Consider Revascularization
  - Aggressive Treatment and Follow-Up of any Ulcers

# DM COMPLICATIONS - SUMMARY

Diabetes is a leading cause of blindness, kidney failure, amputation, heart attack, stroke, and premature death.

# DM COMPLICATIONS - SUMMARY

**These complications can be minimized!**

- Glycemic Control Matters
- **Early Diagnosis of DM**
  - Glycemic Control Matters
- **Monitoring for complications**
  - Glycemic Control Matters
- **Aggressive treatment of co-risk factors**
  - Glycemic Control Matters
- **Team approach - access to multiple specialists**

# DM COMPLICATIONS - SUMMARY

## Glycemic Control Matters*

**Thoughtfully applied in Type 2**

# DM COMPLICATIONS - SUMMARY

**Prevention**
**is more rewarding**
**than**
**Management**
**of Complications**